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(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TROFAST, Jan [SE/SE]; AstraZeneca AB, R & D Lund, S-221 87 Lund (SE). BAUER, Carl-Axel [SE/SE]; AstraZeneca AB, R & D Lund, S-221 87 Lund (SE).

(74) Agent: GLOBAL INTELLECTUAL PROPERTY, PATENTS; AstraZeneca AB, S-151 85 Södertälje (SE).

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(54) Title: NEW COMBINATION OF FORMOTEROL AND MOMETASONE IN A PHARMACEUTICAL COMPOSITION FOR TREATING RESPIRATORY DISORDERS, SUCH AS ASTHMA, RHINITIS AND COPD

(57) Abstract

The invention relates to novel combinations of medicaments useful in the treatment of mild moderate and severe asthma and other respiratory disorders such as rhinitis and chronic obstructive pulmonary disease (COPD).

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NEW COMBINATION OF FORMOTEROL AND MOMETASONE IN A PHARMACEUTICAL COMPOSITION FOR TREATING RESPIRATORY DISORDERS, SUCH AS ASTHMA, RHINITIS AND COPD

Field of the invention

This invention relates to improvement in the treatment of mild and severe asthma and other respiratory disorders such as rhinitis and chronic obstructive pulmonary disease (COPD). More particularly, it relates to the use of the steroidal anti-inflammatory drug mometasone (preferably in the form of its furoate ester) in combination with the long-acting bronchodilator formoterol (preferably as the fumarate dihydrate salt) for the treatment of respiratory disorders such as mild, moderate and severe asthma, rhinitis and COPD, and to pharmaceutical compositions containing the two active ingredients.

Background of the invention

The recognition more than 10 years ago of the fundamentally inflammatory nature of asthma led to the suggestions that control of the underlying airway inflammation could provide the key to the control of asthma at all levels of severity. Nevertheless many patients with asthma of most levels of severity still receive no regular anti-inflammatory treatment and are treated only with intermittent or regular bronchodilator therapy. Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate (BDP) flunisolide, triamcinolone acetonide, dexamethasone, mometasone furoate, fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Long-acting β2-agonists such as formoterol and salmeterol, have different properties from short-acting ones such as terbutaline and salbutamol. These long-acting bronchodilators have been regarded as add-on treatment to steroid therapy. However, the long-acting agonists are considered an alternative to a further increase in the dosage of inhaled steroids. The side-effects of the steroids could therefore be minimized. Therapy should be aimed at

controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

The most common cause for poor control of asthma is poor compliance in the long-time management of chronic asthma, particularly with prophylatic treatment such as inhaled steroids, which do not give immediate symptom relief. Patents will readily take β2-agonist inhalers, since these provide rapid onset of symptoms, but often do not take the prophylactic therapy, such as inhaled steroids, regularly because there is no immediate symptomatic benefit.

Earlier mentioned combinations of long-acting β-agonists and steroids include the use of salmeterol/beclomethasone dipropionate (US 5,208,226), salmeterol/fluticasone propionate (US 5,270,305), formoterol/budesonide (US 5,674,860, Astra) and formoterol/ciclesonide (DE 19541689).

The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects.

Summary of the invention

It has now surprisingly been found that a combination of formoterol and mometasone can be used for the treatment of respiratory disorders such as asthma, rhinitis and COPD. According to the invention there is provided a pharmaceutical combination which comprises formoterol in combination with mometasone.

Detailed description of the invention

The word "combination" is used to describe the invention because the components can be administered simultaneously, sequentially or separately for use in therapy. Thus the active ingredients (a) and (b) are not necessarily, but may be, used as an admixture, they still have the desired effect if they are administered sequentially or separately. Preferably they are not administered more than about two hours apart, for example no more than 30 minutes apart.

The present invention is based on the concept of a novel combination therapy using the long-acting bronchodilator formoterol (preferably as the fumarate dihydrate salt) and the glucocorticosteroid mometasone (preferably as its 17-furoate ester).

In a first aspect the invention therefore provides a pharmaceutical combination comprising:
(a) formoterol, a pharmaceutically acceptable salt or solvate thereof;
(b) mometasone or an ester thereof and optionally a solvate (e.g. mono-hydrate) thereof ; and optionally
(c) one or more pharmaceutically acceptable additives, diluents or carriers;

Preferably the molar ratio of (a) to (b) is from 1:4 to 1:100.

Reference to formoterol and salts and solvates thereof includes all combinations of solvates and salts of formoterol such as solvates of salts.
Preferably the formoterol is in the form of the the fumarate dihydrate salt, nore preferably in the form of the fumarate dihydrate salt of the single R,R-enantiomer.

Preferably the mometasone is in the form of the monohydrate of the furoate ester.

The first main ingredient of the combination of the invention is formoterol, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methyl-ethyl]-amino]-ethyl]phenyl]formamide

or its single R,R-enantiomer. It can be prepared by the methods described in US 5,434,304 (Astra) and DE-A 2,305,092 (Yamanouchi).

The other main ingredient is mometasone (9α,21-dichloro-11β,17-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione)-17-(2'-furoate) or as solvates thereof e.g. as the monohydrate and can be prepared by the methods described in US 4,472,393 or WO 98/00437.

A combination, preferably a fixed combination i.e. given in admixture, of the compounds of the invention will establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalors. This simplifies the life for the patients considerably and makes the life more comfortable and secure.

According to another aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of formoterol or a pharmaceutically acceptable salt or solvate thereof and mometasone or a pharmaceutically acceptable ester thereof (preferably as the monohydrate of the 17-furoate ester) as a preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders such as asthma, rhinitis and COPD. Preferably the combinations of the invention are administered in admixture, that is to say in a single pharmaceutical composition.

The invention additionally relates to the use of formoterol or a pharmaceutically acceptable salt or solvate thereof and mometasone or a pharmaceutically acceptable ester thereof (preferably as the monohydrate of the 17-furoate ester) in the manufacture of pharmaceutical compositions as preparations for simultaneous, sequential or separate administration of formoterol and mometasone (preferably as the monohydrate of the 17-furoate ester) by inhalation in the treament of respiratory disorders such as asthma, rhinitis and COPD.

According to a further aspect of the invention there is provided a method of treating respiratory disorders which comprises the simultaneous, sequential or separate administration by inhalation of effective amounts of formoterol or a pharmaceutically acceptable salt or solvate thereof and mometasone or a pharmaceutically acceptable ester thereof (preferably as the monohydrate of the 17-furoate ester).

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids, such salts as the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluene-sulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballate, hydroxynaphthalenecarboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of that salt.

The intended dose regimen is once or twice a day, where the suitable daily dose of formoterol is in the range of from about 5 to about 250 nmol (preferably from about 15 to about 120 nmol) and for mometasone furoate a daily dose of about 0.1 μmol to about 3 μmol with a preferred dose of about 0.1 μmol to about 2 μmol. The doses of formoterol to mometasone should be selected to be within the molar range of from about 1:4 to about 1:100. The two drugs may be administered separately in the same ratio. The dose of choice will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

The combination can be inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler e.g. multidose reservoir systems from Astra (Turbuhaler®) or Schering-Plough or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs. A diluent or carrier, generally being non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a certain taste can be added to the powdered

medicament in an amount of from 50 μg to 25 mg per dose, more preferably in an amount of from 50 μg to 10 mg, most preferably in an amount of from 100 to 2000 μg.
One or more of the ingredients is preferably in the form of a dry powder, more preferably a micronized dry powder, most preferably an agglomerated micronized dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse particles of the pharmaceutically acceptible additive, diluent or carrier. A fraction of fine particles of carrier may also be present. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is less than 20 μm, preferably less than 10 μm.

When the ingredients of the system are adapted to be administered from a pressurized inhaler (pMDI), they are preferably in micronized form. They are dissolved, or, preferably suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoro-ethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the ingredients of the system of the invention are adapted to be administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The invention is illustrated by the following examples. In the examples, micronization is carried out such that the particle size range for each component is suitable for administration by inhalation. The dry powder formulation containing an additive, diluent or carrier could be either in agglomerated form or as ordered mixtures.

Example 1.	Per dose
Formoterol fumarate dihydrate	12 µg
Mometasone furoate monohydrate	100 µg

Example 2.	
Formoterol fumarate dihydrate	12 µg
Mometasone furoate monohydrate	200 µg

Example 3.	
Formoterol fumarate dihydrate	6 µg
Mometasone furoate monohydrate	100 µg

Example 4.	
Formoterol fumarate dihydrate	6 µg
Mometasone furoate monohydrate	50 µg
Lactose monohydrate	up to 0.5, 1,5,10,20 mg

Example 5.	
Formoterol fumarate dihydrate	6 µg
Mometasone furoate monohydrate	100 µg
Lactose monohydrate	up to 0.5, 1, 5, 10, 20 mg

Example 6.	
Formoterol fumarate dihydrate	6 µg

Mometasone furoate monohydrate	200 µg
Lactose monohydrate	up to 0.5, 1, 5, 10, 20 mg

Example 7.

Formoterol fumarate dihydrate	6 µg
Mometasone furoate monohydrate	100 µg
Oleic acid (based on propellant)	0.005 %
Ethanol (based on propellant)	2 %
Propellant P134a	up to 25, 50 or 100 µl

Example 8.

Formoterol fumarate dihydrate	12 µg
Mometasone furoate monohydrate	200 µg
Oleic acid (based on propellant)	0.01 %
Ethanol (based on propellant)	3 %
Propellant P227/P134a (15/85)	up to 25, 50 or 100 µl

Claims.

1. A pharmaceutical combination which comprises:
(a) formoterol or a pharmaceutical acceptable salt or solvate thereof;
(b) mometasone or an ester thereof, and optionally
one or more pharmaceutically acceptable additives, diluents or carriers.

2. A pharmaceutical combination according to claim 1 wherein the molar ratio of (a) to (b) is from 1:4 to 1:100.

3. A pharmaceutical combination according to claim 1 or 2 in which formoterol is in the form of its fumarate dihydrate salt

4. A pharmaceutical combination according to any one of claims 1 to 3 in which the formoterol is in the form of the single R,R-enantiomer.

5. A pharmaceutical combination according to any one of claims 1 to 4 in which the mometasone 17 is in the form of the furoate ester monohydrate.

6. A pharmaceutical combination according to any one of claims 1 to 5 in which the combination is fixed and given in admixture.

7. A pharmaceutical combination according to any one of claims 1 to 6 in a form suitable for administration from a pressurised inhaler.

8. A pharmaceutical combination according to claim 7 comprising
(a) formoterol or a pharmaceutical acceptable salt or solvate thereof;
(b) mometasone or an ester thereof,
a propellant and one or more other surfactants and/or one or more excipients.

9. A pharmaceutical combination according to claim 8 in which the propellant is HFA 227.

10. A pharmaceutical combination according to any one of claims 1 to 9 for use for the treatment or prophylaxis of a respiratory disorder.

11. A pharmaceutical combination according to any one of claims 1 to 9 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00417

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/58, A61K 31/165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9900134 A1 (ASTRA AKTIEBOLAG), 7 January 1999 (07.01.99) --	1-11
X	WO 9520393 A1 (SCHERING CORPORATION), 3 August 1995 (03.08.95) --	1-11
A	CHIRALITY, Volume 3, 1991, Trofast, Jan et al, "Steric Aspects of Agonism and Antagonism at Beta-Adrenoceptors:" page 443 - page 450 --	3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Information on patent family members

02/12/99

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9900134 A1	07/01/99	AU 8135098 A	19/01/99
WO 9520393 A1	03/08/95	AU 691880 B	28/05/98
		AU 1727195 A	15/08/95
		CA 2182086 A	03/08/95
		CN 1139384 A	01/01/97
		CZ 9602191 A	11/12/96
		EP 0740550 A	06/11/96
		FI 962828 A	12/07/96
		HU 74884 A	28/02/97
		HU 9602043 D	00/00/00
		IL 112459 A	11/04/99
		JP 9501700 T	18/02/97
		NO 963132 A	26/09/96
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		SG 47387 A	17/04/98
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		US 5837699 A	17/11/98
		US 5889015 A	30/03/99
		ZA 9500637 A	26/07/95